Sleep Duration and Snoring in Relation to Biomarkers of Cardiovascular Disease Risk Among Women With Type 2 Diabetes

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OBJECTIVE — Sleep habits have been associated with risk of cardiovascular disease (CVD) and metabolic disturbances, but the mechanisms underlying these associations have yet to be fully elucidated. We aim to determine whether sleep duration and/or snoring are associated with biomarkers of CVD in women with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 935 women aged 43–69 years enrolled in the Nurses' Health Study cohort with type 2 diabetes who had no history of documented coronary heart disease or stroke in 1990. Information on sleep duration and snoring frequency was collected in 1986 from mailed questionnaires, and biomarkers of CVD were measured from blood samples taken in 1989–1990.

RESULTS — Longer sleep duration was associated with increased levels of C-reactive protein after adjusting for age, BMI, lifestyle factors, family history of diabetes, glycemic control, and medication use ($P = 0.05$). HDL was decreased with short and long sleep duration among normotensive ($P = 0.02$) but not hypertensive women. More frequent snoring was directly associated with triglycerides ($P = 0.02$) and inversely associated with HDL cholesterol (0.03) and adiponectin ($P = 0.03$) in multivariate-adjusted analyses.

CONCLUSIONS — The associations of sleep duration and snoring with lipid profile, hormone measures, and/or inflammatory markers may partially explain the previously reported relationship between sleep habits and cardiovascular and metabolic disorders.

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Mounting evidence from epidemiologic research indicates that sleeping habits may play an important role in human health. According to the National Sleep Foundation, mean sleep duration of Americans is estimated at 6.9 h/day (1), and data from 2-week sleep diaries of healthy subjects suggest that sleep duration on weekends is about half an hour longer than on weekdays, possibly indicating compensation for sleep debt (2). Of added concern, the National Sleep Foundation also reports that 56% of Americans snore at least three nights per week, with 24% snoring nearly every night. Of all participants surveyed, 8% had symptoms consistent with a diagnosis of obstructive sleep apnea (OSA) (1). These data underline the high prevalence of sleep deprivation and/or poor quality of sleep in today's society.

Both short (<5 h/day) and long (>9 h/day) duration of sleep have been associated with higher risk of all-cause mortality (3), coronary heart disease (4), and hypertension (5,6). Several large prospective cohort studies, including the National Health and Nutrition Examination Survey (NHANES I) and the Nurses' Health Study (NHS) (7–9), have demonstrated an increased risk of obesity with habitual sleep deprivation. Sleep-disordered breathing has been associated with greater risk of insulin resistance and type 2 diabetes prospectively in NHS (10) and in several smaller cross-sectional studies (11–14), as well as with increased rates of hypertension, stroke, and acute coronary events (15–19). These observational results are consistent with unfavorable changes in glucose tolerance and increases in sympathetic activation demonstrated in experimental sleep deprivation studies (20). However, the biological mechanisms underlying these associations have yet to be fully elucidated, and only a limited number of studies have examined the relationship between sleep habits and established biomarkers of cardiovascular disease (CVD) (8,21–24). Thus, we obtained information on sleep duration and frequency of snoring and measured plasma concentrations of biomarkers of CVD. The objective of our investigation was to determine whether short and/or long sleep duration and, in a separate analysis, snoring are associated with increased total or LDL cholesterol, triglycerides, leptin, or inflammatory markers C-reactive protein (CRP), lipoprotein(a), soluble E-selectin, soluble intercellular adhesion molecule-1 (sICAM-1), and soluble tumor necrosis factor (TNF)-α receptor II and/or decreased HDL cholesterol or adiponectin levels.

RESEARCH DESIGN AND METHODS

— The NHS began in 1976 with the enrollment of 121,700 female nurses between 30 and 55 years of age who received mailed questionnaires every 2 years thereafter on lifestyle factors and health outcomes. From 1989 to 1990, blood samples were obtained from 32,826

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Abbreviations: CRP, C-reactive peptide; CVD, cardiovascular disease; NHS, Nurses' Health Study; OSA, obstructive sleep apnea; sICAM-1, soluble intercellular adhesion molecule 1; TNF, tumor necrosis factor; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

study participants, and among the women who returned blood samples, 1,188 had a confirmed diagnosis of type 2 diabetes. At the time of blood draw, the age of the women ranged from 43 to 69 years. Diagnosis of diabetes was made and validated as previously reported (25), and 74% had a duration of illness >2 years. Women with prior coronary heart disease, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or stroke at blood draw in 1989 or 1990 were excluded from analyses, resulting in a final sample size of 935.

Assessment of sleep duration and snoring frequency

In response to the phrase, "Indicate total hours of actual sleep in a 24-h period" on the 1986 form, participants chose from categories of ≤5, 6, 7, 8, 9, 10, or ≥11 h. Because of the small number of respondents reporting sleep >9 h/day, we created categories of ≤5, 6–7, 8, and ≥9 h for analyses. Frequency of snoring was determined from the item "Do you snore?" with possible responses of "regularly," "occasionally," and "never." The validity of reported sleep habits with 1-week sleep diaries in the NHS cohort have been published previously (3).

Blood collection and processing

Blood was collected and stored in 1989–1990 as previously described (26). Concentrations of total/HDL cholesterol and triglycerides were measured simultaneously on the Hitachi 911 analyzer (Roche, Indianapolis, IN) with coefficients of variation (CVs) <1.8%, and LDL cholesterol was measured using a homogenous direct method (Genzyme, Cambridge, MA) with a CV <3.1%. Adiponectin and leptin were quantified using a radioimmunoassay from Linco Research (St. Charles, MO) with a sensitivity of 2 μg/ml and intra-assay CV of 1.8–6.2% for adiponectin and a sensitivity of 0.5 ng/ml and intra-assay CV of 8.3% for leptin. Plasma CRP was measured using a U.S. CRP enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories, Webster, TX) with a CV range of 2.8–5.1%. Lipoprotein(a) was measured by a latex-enhanced immunoturbidimetric method (Denka Sieken, Tokyo, Japan), with a CV of 2.6%. sICAM-1, soluble E-selectin, and soluble TNF-α receptor II were assayed using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN) with CVs <8.8%.

Assessment of lifestyle exposures

Data on demographic and lifestyle factors were obtained from NHS questionnaires. BMI was calculated from self-reported weight (kilograms) in 1990 divided by height (meters squared) reported in 1976. Reported measurements of waist and hip circumferences were obtained in 1986 and were used to calculate waist-to-hip ratio (WHR). The validity of self-reported anthropometric measures in the NHS has been reported previously, with correlation coefficients ranging from 0.70 to 0.97 (27). Aerobic physical activity in metabolic equivalent tasks per week was computed from 1986 data on duration and intensity of exercises performed (28). Medication use and family history of diabetes were both assessed by the 1988 questionnaire. Smoking status and status of self-reported hypertension and hypercholesterolemia were obtained from questionnaires administered in 1990, and race, marital status, education, and employment were addressed on the 1992 form. Alcohol and caffeine intake were determined from the 1990 questionnaire using a previously validated (29) semiquantitative food frequency questionnaire.

Statistical analysis

Comparisons of continuous demographic, lifestyle, and medical history variables across categories of sleep (≤5, 6–7, 8, and ≥9 h per day) and snoring frequency (never, occasionally, regularly) were conducted using one-way ANOVA and using χ^2 tests for categorical variables. Differences between groups of sleep duration on plasma biomarker concentrations were evaluated using one-way ANOVA, with logarithmic transformation of biomarker level values to achieve normal distribution. Simple and multiple linear regression models were used to detect linear trends among biomarkers with respect to snoring frequency. Potential confounders were adjusted for in multivariate analyses and included age, BMI, WHR, physical activity, smoking, alcohol and caffeine intake, postmenopausal hormone use, aspirin use, insulin and oral diabetes medication use, family history of diabetes, and A1C, with continuous variables categorized in quintiles. We tested for interaction of hypertensive and menopausal status with sleep habits using a multiplicative term and ran stratified analyses where appropriate. Analyses were conducted using the SAS statistical package (Version 8.2 for UNIX; SAS Institute, Cary, NC). A two-sided level of $\alpha = 0.05$ was used to determine statistical significance.

RESULTS — Study population characteristics by hours of sleep per 24 h are presented in Table 1. Women sleeping ≤5 h per 24 h tended to be younger and have higher BMI than women sleeping ≥6 h per night. Short sleepers were more prone to have a family history of diabetes and were marginally more likely to have a history of hypertension compared with women with sleep durations of ≥6 h. Long sleep duration was associated with marginally increased alcohol consumption and greater prevalence of current smoking. Women sleeping ≥9 h had a lower proportion of full-time employment than women sleeping ≤8 h per 24 h (Table 1). When participants were grouped based on snoring frequency (never, occasionally, regularly), women who reported most often snoring tended to be older ($P = 0.03$), have higher BMI ($P < 0.0001$) and WHR ($P < 0.01$) and lower activity levels ($P = 0.03$), reported greater alcohol consumption ($P = 0.04$), were more likely to be hypertensive ($P < 0.0001$), and were less likely to report use of diabetes medication ($P < 0.01$) or diuretics ($P = 0.02$) than women who never snored or snored only occasionally (Table 2).

No differences in biomarker levels among different sleep durations were found in crude analysis (Table 3). After adjusting for age and BMI, CRP concentration was significantly elevated in women sleeping >9 h ($P = 0.01$). Adjusting additionally for lifestyle factors, family history of diabetes, glycemic control, and medication use attenuated the association slightly, but did not diminish the significance of the relationship ($P = 0.05$). Controlling further for WHR did not materially alter reported values (data not shown). Multivariate-adjusted CRP concentrations were 3.9 mg/l for women sleeping ≤5 h and increased to 5.6 mg/l for women sleeping ≥9 h per night ($P = 0.05$). We did not find duration of sleep to be associated with other biomarkers in either crude or adjusted models (Table 3).

We also examined linear associations of mean analyte concentrations by frequency of snoring (Table 4). Snoring frequency was significantly associated with HDL cholesterol, triglycerides, adiponec-

Table 1—*Descriptive characteristics of women with type 2 diabetes* (n = 935) *by duration of sleep*

	Hours of sleep per day				
	≤5	6 or 7	8	≥9	*P**
n	51	600	229	55	
Age (years)	57.9 ± 5.9	58.6 ± 6.8	59.9 ± 6.3	58.7 ± 6.7	0.04
BMI (kg/m^2)	31.6 ± 6.6	30.0 ± 6.4	29.5 ± 5.8	28.4 ± 5.8	0.06
WHR	0.83 ± 0.07	0.84 ± 0.08	0.85 ± 0.07	0.84 ± 0.07	0.47
Physical activity (METs/week)	12.7 ± 21.1	11.8 ± 15.1	11.2 ± 13.9	11.4 ± 17.0	0.92
Alcohol (g/day)	2.4 ± 8.6	2.4 ± 6.1	3.5 ± 9.1	4.5 ± 13.3	0.11
Caffeine (mg/day)	270 ± 298	239 ± 213	249 ± 225	230 ± 199	0.73
Current smoker	8 (16)	83 (14)	23 (10)	13 (24)	0.06
Caucasian	37 (73)	473 (79)	190 (83)	47 (85)	0.21
Married	38 (79)	468 (81)	183 (81)	49 (94)	0.12
Bachelor's degree or higher	12 (24)	150 (26)	43 (19)	11 (21)	0.23
Full-time employment	19 (40)	167 (30)	48 (21)	8 (15)	0.01
Medical history					
Premenopausal	6 (15)	52 (11)	15 (8)	5 (14)	0.43
Hypertension	29 (57)	250 (42)	87 (38)	25 (46)	0.09
Hypercholesterolemia	16 (31)	238 (40)	94 (41)	29 (53)	0.15
Family history of diabetes	37 (73)	298 (50)	121 (53)	24 (44)	0.01
Diabetes medication and control					
Insulin	10 (20)	107 (18)	46 (20)	10 (18)	0.90
Oral diabetes medication	11 (22)	132 (22)	59 (26)	6 (11)	0.12
A1C	7.0 ± 1.8	6.9 ± 1.8	7.0 ± 1.7	6.7 ± 1.4	0.73
Other medication use					
Postmenopausal hormones	9 (18)	198 (33)	80 (35)	22 (41)	0.07
Aspirin	17 (33)	262 (44)	114 (50)	25 (46)	0.15
Thiazide diuretics	13 (25)	194 (32)	77 (34)	17 (31)	0.73
Other hypertension medication	4 (8)	56 (9)	21 (9)	7 (13)	0.83
β-Blocker	7 (14)	96 (16)	38 (17)	12 (22)	0.68
ACE inhibitor	7 (14)	54 (9)	21 (9)	4 (7)	0.68
Calcium channel blocker	3 (6)	30 (5)	13 (6)	3 (6)	0.98
Cholesterol-lowering medication	1 (2)	25 (4)	12 (5)	5 (9)	0.28

Data are means ± SD or *n* (%). **P* value from one-way ANOVA for continuous measures and χ^2 test for categorical variables. Nonparametric Kruskal-Wallis tests yielded similar results to ANOVA (not shown). METs, metabolic equivalent tasks.

tin, leptin, CRP, soluble E-selectin, and soluble TNF-α receptor II (all $P < 0.05$) and marginally with sICAM-1 ($P = 0.06$). Controlling for age and BMI attenuated these relationships, but associations of snoring with HDL cholesterol, triglycerides, adiponectin, and leptin remained statistically significant. These associations also persisted after multivariate adjustment for additional variables, although the trend between snoring and leptin became marginal ($P = 0.10$). Adjusting further for WHR did not appreciably change these results (not shown). HDL cholesterol decreased linearly with reports of more frequent snoring from 53 mg/dl in women reporting never snoring to 50 mg/dl in those reporting regular snoring ($P = 0.03$), and triglycerides increased from 137 to 163 mg/dl ($P = 0.02$). In addition, adiponectin decreased from 7.7 to 6.4 μg/ml ($P = 0.03$), and leptin increased from 39.8 to 45.9 ng/dl ($P = 0.10$) (Table 4).

We found no significant interaction between menopausal status and sleep duration or snoring ($P > 0.05$ for all). There was evidence of a differential association between sleep duration and HDL concentration by hypertensive status (*P* for interaction = 0.008). Stratified analyses revealed significant differences in HDL between sleep duration groups among normotensive women, with mean levels of 49.8 mg/dl for women sleeping <5 h, 50.1 mg/dl for 6–7 h, 54.4 mg/dl for 8 h, and 47.8 mg/dl for ≥9 h ($P = 0.02$). No significant differences in HDL were detected among hypertensive women ($P > 0.10$). We found no evidence of interaction between sleep duration or snoring and hypertension in predicting any other biomarker ($P > 0.10$ for all).

CONCLUSIONS — Research over the past several years indicates that both short and long sleep duration as well as snoring are associated with the development of cardiovascular and metabolic disorders (4,10–15,17–19,30,31). Our results suggest that these effects may be related to associations of sleep duration and snoring with serum concentrations of certain biomarkers of CVD risk among women with type 2 diabetes.

The biological mechanisms underlying the relationship between sleep and cardiovascular-related conditions remain to be fully elucidated, and associations of sleep habits with biomarkers of CVD have not been thoroughly examined. Much of the emphasis of prior research regarding sleep duration and cardiovascular-related outcomes has focused on the adverse effects of sleep deprivation. Short-term sleep restriction to 4 h per day for several

Table 2—*Descriptive characteristics of women with type 2 diabetes* (n = 935) *by frequency of snoring*

	Snoring status			
	Never	Occasionally	Usually	*P*
n	116	613	200	
Age (years)	57.4 ± 7.7	59.0 ± 6.4	59.2 ± 6.5	0.03
BMI (kg/m^2)	26.2 ± 5.2	29.7 ± 6.1	32.5 ± 6.1	<0.0001
WHR	0.81 ± 0.12	0.84 ± 0.09	0.85 ± 0.09	0.005
Activity (METs/week)	15.2 ± 19.9	11.4 ± 14.5	10.7 ± 14.7	0.03
Alcohol (g/day)	2.5 ± 5.5	2.4 ± 6.4	4.0 ± 11.3	0.04
Current smoker	15 (13)	91 (15)	21 (11)	0.30
Caucasian race	87 (75)	496 (81)	162 (81)	0.38
Married	93 (82)	482 (81)	162 (84)	0.75
Bachelor's degree or higher	26 (23)	146 (25)	43 (22)	0.41
Full-time employment status	34 (30)	155 (26)	51 (26)	0.72
Medical history				
Premenopausal	17 (20)	45 (9)	15 (10)	0.02
Hypertension	29 (25)	263 (43)	98 (49)	0.0001
Hypercholesterolemia	41 (35)	249 (40)	87 (43)	0.38
Family history of diabetes	57 (49)	321 (52)	99 (49)	0.91
Diabetes medication and control				
Insulin	27 (23)	122 (20)	22 (11)	0.006
Oral diabetes medication	17 (15)	143 (23)	47 (23)	0.11
A1C (%)	6.6 ± 1.7	6.9 ± 1.7	7.0 ± 1.9	0.15
Other medication				
Postmenopausal hormones	44 (39)	206 (34)	59 (29)	0.24
Aspirin	45 (39)	279 (45)	92 (46)	0.40
Thiazide diuretics	24 (21)	208 (34)	69 (34)	0.02
Other hypertension medication	6 (5)	62 (10)	20 (10)	0.24
β-Blocker	12 (10)	103 (17)	38 (19)	0.13
ACE inhibitor	7 (6)	61 (10)	18 (9)	0.41
Calcium channel blocker	2 (2)	34 (6)	12 (6)	0.20
Cholesterol-lowering medication	4 (3)	33 (5)	6 (3)	0.31

Data are means ± SD or *n* (%). **P* value from one-way ANOVA for continuous measures and χ^2 test for categorical variables. Nonparametric Kruskal-Wallis tests yielded similar results as ANOVA (not shown). METs, metabolic equivalent tasks.

days has been shown to increase sympathetic nervous system activity and result in elevated concentrations of CRP, interleukin-6, and TNF-α (20–22). To our knowledge, no studies to date have examined causes of increased cardiovascular and metabolic disease, including levels of biomarkers of CVD, among individuals with long sleep duration. In our study, we found higher levels of CRP in women sleeping ≥9 hours, providing a novel biological explanation for the poorly understood relationship between extended sleep and cardiovascular morbidity and mortality. CRP is a hepatocyte protein whose synthesis is mediated by interleukin-6 and TNF-α and displays little circadian variability (21). It is the primary marker of protein formation in response to inflammatory stimuli and has been shown to predict stroke and myocardial infarction. CRP may be directly implicated in atherosclerosis by promoting endothelial secretion of inflammatory mediators and increasing macrophage uptake of LDL (21). Proinflammatory cytokines have been shown to be elevated in conditions of obesity and insulin resistance and are believed to also play key roles in sleep pathology, such as sleep apnea and fatigue. The sleep-inducing effects of proinflammatory cytokines are presumed to be an evolutionary adaptation to promote recovery from illness (32). Thus, a possible mechanism explaining the observed associations between CRP, CVD, and long sleep duration in individuals with diabetes may be that increased proinflammatory cytokines induce sleep and in parallel raise CRP concentrations that promote the development of CVD.

Sleep-disordered breathing and OSA have also been independently associated with cardiovascular and metabolic disturbances in both men and women (10–15,17–19,31). OSA, which is characterized by cessation of airflow during sleep due to upper airway collapse, has been shown to acutely increase both vascular sympathetic nerve activity and arterial blood pressure (16,33), and chronic effects of OSA include glucose intolerance, hypertension, and atherosclerosis due to oxidative stress, sympathetic activation, endothelial dysfunction, and inflammation (10,16,34). Previous case-control (35) and OSA treatment intervention (36) studies have found significant positive associations between OSA and adhesion molecules, and additional case-control studies have linked OSA with increased levels of CRP, interleukin-6, and TNF-α (37,38). Crude analysis of our data showed increased CRP, soluble E-selectin, sICAM-1, and soluble TNF-α receptor II with more frequent snoring, but after adjusting for age and BMI, these associations became nonsignificant. However, significant associations of sleep-disordered breathing with HDL, triglycerides, and adiponectin persisted after adjustment for age and BMI, as well as for additional lifestyle and medical confounders. Prior research on the association between OSA and lipid abnormalities has yielded mixed results, with many positive and negative studies, but there is building evidence that the relationship may differ by sex. Consistent with our findings, previous studies have demonstrated low HDL (39) and elevated triglycerides (40) in women, but not men, with sleep-disordered breathing. Chronic elevation of sympathetic activity may be responsible for the unfavorable lipid profile observed in OSA. Some (41,42) but not all (31) prior cross-sectional studies have demonstrated decreased concentrations of adiponectin in OSA, and it is possible that the increased glucose intolerance and risk of type 2 diabetes observed in OSA may be related to low adiponectin. Similarly, elevated leptin levels have also been previously observed in OSA (43,44). Our results support a role of adverse levels of HDL, triglycerides, adiponectin, and possibly leptin in individuals reporting more frequent snoring in mediating the previously reported increased risk of type 2 diabetes (10) and CVD (19,45).

Because both sleep duration and snoring are strongly correlated with overweight and obesity (7,10,14,16,46,47), it is often proposed that confounding by BMI might explain associations of sleep habits with cardiovascular and metabolic

Table 3—*Crude and adjusted measures of biomarkers by sleep duration*

	Hours of sleep per day				
	≤5	6 or 7	8	≥9	*P**
n	51	800	229	55	
Lipid profile					
Total cholesterol (mg/dl)	218 ± 1.3	223 ± 1.2	221 ± 1.2	229 ± 1.2	0.59
Age and BMI adjusted	215	223	219	228	0.33
Multivariate adjusted†	217	221	218	224	0.62
HDL cholesterol (mg/dl)	48 ± 1.3	49 ± 1.3	50 ± 1.3	50 ± 1.3	0.51
Age and BMI adjusted	48	48	49	48	0.62
Multivariate adjusted†	52	51	53	51	0.63
LDL cholesterol (mg/dl)	130 ± 1.4	134 ± 1.4	133 ± 1.4	136 ± 1.4	0.87
Age and BMI adjusted	128	134	132	138	0.66
Multivariate adjusted†	130	131	130	133	0.96
Triglycerides (mg/dl)	176 ± 2.0	173 ± 1.8	165 ± 1.8	181 ± 1.8	0.63
Age and BMI adjusted	171	176	164	186	0.37
Multivariate adjusted†	152	157	146	162	0.35
Hormones					
Adiponectin (μg/ml)	5.4 ± 2.0	5.8 ± 2.0	6.0 ± 2.0	5.0 ± 2.0	0.51
Age and BMI adjusted	5.5	5.4	5.6	4.7	0.39
Multivariate adjusted†	7.0	6.8	7.0	5.9	0.44
Leptin (ng/ml)	40.0 ± 2.3	37.0 ± 2.2	35.0 ± 2.4	35.0 ± 2.2	0.66
Age and BMI adjusted	41.1	43.7	41.2	45.1	0.56
Multivariate adjusted†	41.6	45.1	43.0	46.7	0.63
Inflammatory markers					
CRP (mg/l)	3.8 ± 2.4	3.8 ± 2.5	3.7 ± 2.5	5.0 ± 2.7	0.24
Age and BMI adjusted	3.8	4.3	4.2	6.1	0.01
Multivariate adjusted†	3.9	4.1	3.9	5.6	0.05
Lipoprotein(a) (mg/dl)	7.2 ± 4.2	7.9 ± 3.8	8.6 ± 4.3	7.0 ± 2.9	0.66
Age and BMI adjusted	6.9	7.6	8.3	6.7	0.63
Multivariate adjusted†	7.7	8.5	9.0	7.9	0.85
Soluble E-selectin (ng/ml)	57.0 ± 1.6	58.5 ± 1.6	59.7 ± 1.7	52 ± 1.7	0.33
Age and BMI adjusted	57.4	61.5	63.0	56.5	0.35
Multivariate adjusted†	48.7	54.2	55.9	49.2	0.12
sICAM-1 (ng/dl)	304 ± 1.4	299 ± 1.4	300 ± 1.3	292 ± 1.3	0.92
Age and BMI adjusted	303	301	301	294	0.97
Multivariate adjusted†	283	283	284	274	0.91
Soluble TNF-α receptor II (pg/ml)	2,405 ± 1.4	2,422 ± 1.3	2,463 ± 1.4	2,539 ± 1.3	0.62
Age and BMI adjusted	2,476	2,486	2,510	2,642	0.47
Multivariate adjusted†	2,449	2,541	2,547	2,682	0.43

Data are variable geometric means ± SE unless otherwise indicated. **P* value from one-way ANOVA. Nonparametric Kruskal-Wallis tests produced similar results. †Multivariate model included age, BMI, physical activity, smoking, alcohol and caffeine intake, postmenopausal hormone use, aspirin use, insulin and oral diabetes medication use, family history of diabetes, and A1C.

disorders. However, the statistical significance of the associations reported herein account for variation in BMI, as well as additional lifestyle and medical factors. Controlling further for WHR did not substantially alter reported values. While we saw similar associations for pre- and postmenopausal women, the small proportion of premenopausal women limits the generalizability of our results to this population, as well as to women without diabetes or to men. Future studies may also consider the impact of polycystic ovarian syndrome, which has been associated with premenopausal insulin resistance and OSA (48,49) but was not diagnosed in our study. The possibility remains that measurement error due to collecting covariate data at different time points and/or circadian variability from non-uniform timing of blood sampling may have introduced a degree of random misclassification, skewing reported associations toward the null. Use of more precise measures of sleep-related variables, such as polysomnographies, may reduce variability, but these techniques are logistically unfeasible to perform in large epidemiology studies, such as ours. Although women with baseline coronary heart disease or stroke were excluded from the study, reverse causality cannot be withheld as an explanation of reported associations, since it is possible that preexisting undiagnosed cardiovascular morbidity may have influenced sleeping patterns.

In summary, our results suggest that inflammatory processes including increased CRP and, in normotensive women, decreased HDL may contribute to the previously observed association between sleep duration and increased cardiovascular morbidity and mortality in women with type 2 diabetes. Alterations in lipid profile and adiponectin levels may explain in part the metabolic and cardiovascular disturbances associated with frequent snoring. These findings further

Table 4—*Crude and adjusted measures of biomarkers by snoring frequency*

	Snoring frequency			
	Never	Occasionally	Regularly	*P**
n	116	613	200	
Lipid profile				
Total cholesterol (mg/dl)	213 ± 1.2	224 ± 1.2	224 ± 1.2	0.12
Age and BMI adjusted	215	223	221	0.32
Multivariate adjusted†	215	221	219	0.60
HDL cholesterol (mg/dl)	53 ± 1.4	50 ± 1.3	46 ± 1.3	<0.0001
Age and BMI adjusted	51	49	46	0.006
Multivariate adjusted†	53	52	50	0.03
LDL cholesterol (mg/dl)	128 ± 1.3	134 ± 1.4	133 ± 1.4	0.18
Age and BMI adjusted	131	134	132	1.00
Multivariate adjusted	130	132	129	0.71
Triglycerides (mg/dl)	137 ± 1.8	173 ± 1.8	193 ± 1.7	0.003
Age and BMI adjusted	147	173	186	0.001
Multivariate adjusted†	137	154	163	0.02
Hormones				
Adiponectin (μg/ml)	7.4 ± 2.1	5.9 ± 2.0	4.9 ± 1.8	<0.0001
Age and BMI adjusted	6.3	5.5	4.9	0.002
Multivariate adjusted†	7.7	6.9	6.4	0.03
Leptin (ng/ml)	23.5 ± 2.5	36.6 ± 2.3	46.9 ± 1.9	<0.0001
Age and BMI adjusted	37.5	43.4	44.9	0.03
Multivariate adjusted†	39.8	44.5	45.9	0.10
Inflammatory markers				
CRP (mg/l)	2.7 ± 2.4	3.8 ± 2.5	4.5 ± 2.4	0.0001
Age and BMI adjusted	3.9	4.4	4.4	0.32
Multivariate adjusted†	3.9	4.1	4.1	0.59
Lipoprotein(a) (mg/dl)	7.7 ± 3.9	8.2 ± 3.9	7.5 ± 3.7	0.82
Age and BMI adjusted	7.2	7.8	7.5	0.95
Multivariate adjusted†	7.8	8.7	8.4	0.76
Soluble E-selectin (ng/ml)	50.0 ± 1.6	59.3 ± 1.6	60.8 ± 1.6	0.008
Age and BMI adjusted	56.3	62.6	60.6	0.39
Multivariate adjusted†	51.1	55.2	52.5	0.96
sICAM-1 (ng/dl)	281 ± 1.3	301 ± 1.4	303 ± 1.4	0.06
Age and BMI adjusted	286	303	300	0.33
Multivariate adjusted†	270	285	282	0.42
Soluble TNF-α receptor II (pg/ml)	2,293 ± 1.3	2,444 ± 1.3	2,505 ± 1.3	0.03
Age and BMI adjusted	2,421	2,508	2,511	0.35
Multivariate adjusted†	2,507	2,540	2,549	0.65

Data are variable geometric means ± SE unless otherwise indicated. **P* value from linear regression models of log-transformed variables to test for linear trends. †Multivariate model included age, BMI, physical activity, smoking, alcohol and caffeine intake, postmenopausal hormone use, aspirin use, insulin and oral diabetes medication use, family history of diabetes, and A1C.

clarify and emphasize the impact of sleep habits on cardiovascular biology.

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